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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/749,728	12/28/2000	Akihiro Umezawa	766.43	6784

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EXAMINER
SHUKLA, RAM R

ART UNIT	PAPER NUMBER
1632	18

DATE MAILED: 12/12/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/749,728	UMEZAWA ET AL.	
	Examiner	Art Unit	
	Ram R. Shukla	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-91* is/are pending in the application.

4a) Of the above claim(s) *47-75 and 78-91* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-46,76 and 77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *16* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election with traverse of the invention of group I (claims 1-46 and 76-77) and election of species to cardiomyocytes (claim 5), human (claim 24), cytokine (claim 30) and midkine (claim 31) in Paper No. 17 is acknowledged. The traversal is on the ground(s) that groups VI is simply a used of the cells of group I. This is not found persuasive because as noted in the previous office action of 8-7-02, product and process of use can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, in the instant case the invention of group I is drawn to a cell, whereas the inventions of the groups II, III and VI-XII are drawn to various methods that have distinct steps and the methods steps are not co-extensive, although all the methods use the cell of group I. For example, the method of screening for a factor for cardiomyocyte differentiation would be different from a method of screening for a factor for adipocyte differentiation, since the step of monitoring cell differentiation would be different and distinct for a cardiomyocyte and an adipocyte. The criteria used in monitoring the adipocyte differentiation can not be used in evaluating cardiomyocyte differentiating. Accordingly, the methods of groups II, III and VI-XII are patentably distinct each from the other and they would require a separate and non-coextensive search in the patent and non-patent literature. Applicant' statement regarding Commissioner's Official Gazette of March 4, 1996 is acknowledged.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 47- 75 and 78-91 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 17.

3. Claims 1-46 and 76-77 are under consideration.

4. Claims 4-18 and 20-46 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only and cannot depend from any other multiple dependent claim See MPEP § 608.01(n). In the interest of compact prosecution, these claims have been considered given best interpretation possible. Applicants are advised to correct the dependency problems for the response to this action to be complete.

Priority

5. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Japan on Pat Hei.11-372826 filed 12-28-1999 and PCT/JP00/01148, filed 2-28-00. It is noted, however, that applicant has not filed a certified copy of these applications as required by 35 U.S.C. 119(b).

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 76 and 77 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided

by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

Claimed invention is drawn to a method of regenerating a heart damage by using a cell that can differentiate into a cardiomyocyte and an agent for cardiac regeneration.

The specification as filed is not enabling for a method of regenerating heart damage in a heart disease because the art of treatment using a pluripotent stem cell is unpredictable as evidence by the art of record discussed below and the specification does not provide sufficient guidance as to how an artisan of skill would have practiced the claimed invention without undue experimentation.

It is noted that at the time of the invention, the art of using stem cells to treat any condition other than that of hematopoietic cells was not routine and is not routine even today. There is no evidence in the art or in the specification that using any cell that can differentiate into cardiomyocyte one can treat a disease. Most importantly, a cell that is pluripotent when introduced in a patient will differentiate in every type of tissue it can differentiate into and therefore, the resultant cells will form a teratoma (see Klug et al second paragraph in the right column on page 216). Furthermore, Klug et al noted: "while it remains to be established if any form of cellular engraftment can effect myocardial repair (see reference 26 for a critical review), it is virtually certain that human fetal donor cariomyocytes can not be obtained in sufficient numbers for use in a clinical setting." Therefore, at the time of the invention, the treatment of disease with a cell that differentiated into cardiomyocytes and that resulted in treatment or myocardial repair was not

established. In addition to this, transplantation of any allogeneic or xenogeneic cells for treating a heart disease was also not routine in the art and an artisan of skill would not have know as to whether allogeneic or xenogeneic cells would have survived in a patient. Additionally, there is no teaching how many cells would have been transplanted or administered for effecting treatment, how will the cells be administered to a patient, whether sufficient number of cells will reach the site of damage, whether the cells will differentiate into cardiomyocytes and whether the resultant cardiomyocytes will function as heart muscle cells and treat the damage, how would an agent be administered to a patient to ensure that sufficient agent would reach site of heart damage and would cause differentiation of the cells to only cardiomyocytes, not to neural cells or to hepatocytes or any other cell type.

Mayer et al (American Journal of Heart 134:577-586, 1997) noted about myocardial grafting:

"If cells within the heart are induced to proliferate, it would be imperative to turn off replication after a sufficient level of repopulation. Uncontrolled proliferation in situ or metastasis from dividing or grafted cells would be unacceptable. Augmenting cardiomyocyte numbers is necessary but not sufficient for the goal of increasing effective myocardial mass; the new myocytes must be functional with properties that include contractile phenotype and integration into the electrical and mechanical activity of the heart. If they do not work in conjunction with existing myocytes, they may create a nonfunctional scar, predisposing to ventricular modeling, dilation, worsening heart failure, and arrhythmias."

There is no evidence of record that the cells transplanted as claimed will function as heart cells in terms of contractile phenotype and integration into electrical and mechanical activity of the heart and that they will work in conjuction with the existing myocytes. It is reiterated that the art of cell transplantation was not routine in the art for treating heart disease by administering any stem cell to a patient along with an agent that causes differentiation of these cells in to cardiomyocytes and the specification as filed does not provide sufficient guidance for an artisan to address the enablement issues raised above and therefore an artisan of skill would have required extensive experimentation to figure out and

address the issues raised above. Such experimentation would have been undue because neither the art nor the specification at the time of the invention taught how to perform such experimentation.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-46 and 76-77 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because it recites the term "a cell .....which has the potential..." It is noted that the metes and bounds of the claimed invention is not clear since the metes and bounds of the term "potential" are not defined.

Claims 4-18 and 20-46 are indefinite because they are multiple dependent claims and therefore, their metes and bounds of the claimed invention are not clear.

Claims 9-14 are indefinite as discussed below. Claims 9 and 12 are indefinite because they are dependent on claim 8, however one of these claims recites a CD34 positive cell whereas the other one recites a CD34 negative cell. It is not clear as to how a cell can be both positive and negative for a certain receptor. Similarly claims 11 is dependent on claim 9 which is dependent on claim 8, however, claim 8 recites a cell that is CD140 positive and then claim 11 recites a cell that is CD140 negative. Claims 10 and 14 are indefinite for same reasons. It is not clear how the same cell is first positive for a receptor and then becomes negative. Applicants are advised to present claims that clearly recite the claimed invention.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1-46 are rejected under 35 U.S.C. 102(b) as being anticipated by Klug et al (Genetically selected cardiomyocytes from differentiating embryonic stem cells form stable intracardiac grafts. Journal of Clinical Investigation. 98:216-224, 1996).

Claimed invention is directed to a cell that has the potential to differentiate into at least a cardiomyocyte. Other dependent claims recite markers for which the cell is positive or negative or a method by which cell is differentiated to make cardiomyocytes or other cell types.

Klug et al teaches ES cells that differentiate into cardiomyocytes (see the method sections on page 217, first full paragraph in the left column). It is noted that all the characteristics recited in different claims will be inherent to these cells because these are pluripotent cells and based on the condition of culture will differentiate into different cell type. Therefore, the claimed invention is anticipated by Klug et al.

12. Claims 1-46 are rejected under 35 U.S.C. 102(b) as being anticipated by Juttermann et al (Proc. Natl. Acad. Sci. USA. 91:11797-11801, 1991).

Juttermann et al teaches ES cells and the effect of 5-azadCyd on these cells. It is noted that while this art does not teach differentiation of these cells into cardiomyocytes or other cell types, it is emphasized that the claims are drawn to a cell that has a potential to differentiate into different cell as recited, the cells of Juttermann et al will meet the limitations since all the markers recited will be inherent properties of the cells because these are pluripotent ES cells and based on the condition of culture will differentiate into different cell type. Therefore, the claimed invention is anticipated by Juttermann et al.

13. Claims 1-46 are rejected under 35 U.S.C. 102(b) as being anticipated by Pinney et al (Environmental Health Perspectives 80:221-227, 1989).

Pinney et al teaches ES cells which when exposed to 5-azacytidine are differentiated into chondrogenic and adipogenic lineages (see the abstract). It is noted that while this art does not teach differentiation of these cells into cardiomyocytes, it is emphasized that the claims are drawn to a cell that has a potential to differentiate into different cell as recited, the cells of Pinney et al will meet the limitations since all the markers recited will be inherent properties of the cells because these are pluripotent ES cells and based on the condition of culture will differentiate into different cell type. Therefore, the claimed invention is anticipated by Pinney et al.

14. Claims 1-46 are rejected under 35 U.S.C. 102(b) as being anticipated by Shi et al (Blood 92:362-367, 1998)).

Shi et al teaches derivation of endothelial cells from bone marrow cells and growth and differentiation of the bone marrow cells in presence different growth factors and expression of markers by these cells (see the entire article). It is noted that the claims are drawn to a cell that has a potential to differentiate into different cell as recited, the cells of Pinney et al will meet the limitations since all the markers recited will be inherent properties of the cells because these are bone marrow cells and based on the condition of culture will differentiate into different cell type. Therefore, the claimed invention is anticipated by Shi et al.

15. Claims 1-46 are rejected under 35 U.S.C. 102(a) as being anticipated by Young et al (Proceedings of the Society of Experimental Biology and Medicine. 221:63-71, 1999)).

Young et al teaches human pluripotent ad progenitor cells and growth and differentiation of these cells in presence different growth factors and expression of markers by these cells (see the entire article). It is noted that the claims are drawn to a cell that has a potential to differentiate into different cell as recited, the cells of Young et al will meet the limitations since all the markers recited will be inherent properties of the cells because these are bone marrow cells and based on the condition of culture will differentiate into different cell type. Therefore, the claimed invention is anticipated by Young et al.

16. Claims 1-46 are rejected under 35 U.S.C. 102(a) as being anticipated by Makino et al (Journal of Clinical Investigation. 103:697-705, 1999).

This art teaches that cardiomyocytes can be generated from arrow stromal cells in vitro (see the entire article). Therefore, the claimed invention is anticipated by Makino et al.

17. No claim is allowed.

When amending claims, applicants are advised to submit a clean version of each amended claim (without underlining and bracketing) according to § 1.121(c). For instructions, Applicants are referred to http://www.uspto.gov/web/offices/dcom/olia/aipa/index.htm.

Applicants are also requested to submit a copy of all the pending/under consideration claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Tiffiany N. Tabb whose telephone number is (703) 605-1238.

Ram R. Shukla, Ph.D.

RAM R. SHUKLA, PH.D
PATENT EXAMINER